201-14719

Petroleum HPV

September 2, 2003

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

HPV Challenge Program, AR-201
HPV Consortium

Re: Response to Comments on Gasoline Blending Streams Test Plan

Dear Administrator,

The Petroleum HPV Testing Group is a consortium representing 92 percent of the nation's petroleum refining capacity. The Group is made up of 70 member companies of the American Petroleum Institute (API), the National Petrochemical and Refiners Association (NPRA), the Gas Producers Association (GPA) and the Asphalt Institute. The Testing Group appreciates the comments received on its Test Plan for Gasoline Blending Streams that was submitted on December 20, 2001 and posted on the Agency's ChemRTK website on January 25, 2002. The Environmental Protection Agency (EPA), the Environmental Defense (ED), and the Physicians Committee for Responsible Medicine (PCRM) submitted comments on this Test Plan. In the interest of communicating our intent with all interested stakeholders, the Testing Group is providing a revised test plan and robust summaries for posting on the ChemRTK website. In addition, the two sets of documents will be posted on our website, www.petroleumhpv.org.

PCRM and ED expressed the opinions that the test plan met both the spirit and substance of the HPV Challenge program. Indeed, PCRM suggested that, considering the extensive data base on gasoline and its component streams, additional testing on the high naphthenic stream may be unnecessary and data gaps could be filled by read-across from available data on gasoline and related solvents [Letter to C. Whitman, 5/24/2002].

The Testing Group was pleased that, in general, EPA found our approach to evaluating toxicity of Gasoline Blending streams to be appropriate and agreed with our testing proposals. The major issues to be addressed and the Testing Group's responses are presented here.

General

The EPA commented that the submitter presented a generally thorough and well-written test plan. However, EPA felt that clarity was impaired by some inconsistencies in describing composition [e.g. use of wt% and vol% in characterizing composition], and in many cases found it difficult to link test substances in robust summaries with corresponding discussions in the test plan text.

> With the exception of figure 3 (p. 7 of test plan), which illustrates distribution of PONA classes in wt%, all other composition descriptions are presented as vol%. When a stream is comprised primarily of lighter hydrocarbons (e.g. paraffins) vol% and wt% are nearly identical. In general in converting from vol% to wt% for other classes, % paraffin becomes slightly lower (by 2-6%) and the heavier % aromatics become slightly higher (by 1-6%).

However, these variations are not substantial enough to impact toxicological results of studies performed over a range of dose levels.

To facilitate the linking of test materials in robust summaries with discussions of these materials and test results in the test plan, compositional descriptions of individual test materials in Section 1.1 of the IUCLID data set have been expanded and cross-referenced with test summaries.

EPA noted that robust summaries were not always provided for mammalian and environmental studies discussed in the test plan. Examples of studies mentioned in the test plan but for which no summaries were provided included: olefinic (two repeated dose studies and one genotoxicity study); naphthenic naphtha (acute fish, invertebrate, and alagae); and aromatic naphthenes (two repeated dose studies, four genotoxicity studies, and acute fish and daphnid studies). EPA also noted in the case of the ecotoxicity studies citations had not been provided.

The approach of the Testing Group in preparing test plans for petroleum materials under the voluntary HPV program has always been to review available toxicology studies, address all scientifically adequate information in the toxicology summary of the test plan with appropriate citations, but prepare robust summaries on the one study or several studies that best address each critical endpoint of interest for HPV. Other studies would be cited in the comments section. The IUCLID summaries were rechecked with the test plan and robust summaries of critical studies that had been inadvertently omitted were added; other study citations were added as appropriate.
The rationale for omitting robust summaries on several studies cited by EPA, is explained as follows:

Olefinic mammalian studies: Two repeat dose studies (Lapin et al., 2001; Dalbey, 1996) were included in the original summaries and considered adequate for the repeated dose endpoint. The two missing studies referred to by EPA are an API study (1987) and a study by Halder et al (1984). The Halder study concerns renal effects that are irrelevant for man, and as a consequence, was not included in the original robust summaries. The API study adds nothing to what is already described in these summaries. However descriptions and references have been added to the remarks section of the revised summary for the Dalbey et al. (1996) study. All four missing genotoxicity studies have been added to the revised set of summaries (API, 1985; API, 1985; API, 1987; API, 1988).

Aromatic mammalian studies: Three 13-week studies were included in the original robust summaries (API, 1986; Dalbey and Feuston, 1996; Schreiner et al., 2000). Those missing were two 21-day studies by Halder et al (1984), neither of which are relevant for man; since they were also only 21-days in length they did not contribute any more information than already provided in the 13-week studies. EPA is correct concerning the other missing genetic toxicity studies (API, 1985; API, 1985; API, 1985; API, 1986; API, 1986); they have been included in the revised robust summaries for high aromatic naphtha.

Ecotoxicity studies: Citations for the ecotoxicity studies have been included in the test plan, however, since a data review had already been conducted by scientific experts in the CONCAWE organization, no additional review was done. Due to the lack of experimental detail in the published CONCAWE report [CONCAWE, 1996; Report No. 96/52], the Testing Group was unable to assign a Klimisch reliability score to the report. However, the Testing Group thinks the information is consistent with similar tests on other similar petroleum hydrocarbons in these categories and is of sufficient quality to allow it to be used to fulfill the data needs for these endpoints.

Category Definition

EPA requested clarification on the relationship of light hydrocracked naphtha and sweetened naphtha with the heavy straight run naphtha, the suggested test sample for the high naphthenic class.

> Naphthenes (cycloparaffins) are present in gasoline and most finished blending streams at similar concentrations (5-10%). Unlike the other classes, cycloparaffin streams are rarely isolated and are usually fed directly into gasoline blends. The highest likely concentration of naphthenes in this intermediate stream could be in the range of ±30% if such a stream were available (e.g. heavy straight run naphtha). Light hydrocracked naphtha (26.1 vol% naphthehic) and sweetened naphtha (20.9 vol% naphthenic) are presented as relatively high naphthenic streams for which some data are available to address acute toxicity, genetic toxicity, and some ecotoxicity endpoints. Since there is insufficient information from these streams to complete characterization of the high naphthenic group for repeated dose and reproductive/developmental toxicity, a test stream in the range of ± 30% naphthenics will be sought for proposed testing. A short discussion has been added to p. 8 of the test plan to address this issue.

Category Justification

EPA agreed with the justification for grouping 87 blending streams in this category and with the use of PONA (**P**araffinic, **O**lefinic, **N**aphthenic, and **A**romatic) content to organize the streams into sub-groups.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility). EPA requested more complete information on boiling point, vapor pressure ranges, partition coefficients, and water solubility to better characterize streams in general and individual materials.

> Additional component information has been added to Section 1.1 of the IUCLID data sets.

Environmental Fate (photodegradation, biodegradation, fugacity, stability in water).

Biodegradation. EPA agreed with the performance of a biodegradation test on a representative high naphthenic stream but suggested analysis of individual components during the course of the study.

> The Testing Groups believes that analysis of individual components in these complex petroleum streams would be technically arduous, costly and unnecessary. This analysis is not required as part of the basic SIDS data set, additionally there are literature citations included as robust summaries adequately detailing the primary degradation of hydrocarbon components in a laboratory blended gasoline (Solarno-Serena, 1999).

Transport and Distribution. EPA recommended that a Level III fugacity calculation be employed rather than Level I.

> The Testing Group supports the use of a Level I fugacity calculation. Expert modeling scientists from the Center for Environmental Modeling, Trent University, Toronto, Canada have stated that Level 3 fugacity predictions are inappropriate for complex mixtures. Therefore, Testing Group developed test plans for petroleum substances that are, with minimal exception, characterized as complex, heterogeneous mixtures consisting of

chemicals from different alkyl and aryl hydrocarbon classes. Due to the variability in hydrocarbon number and hydrocarbon type for the chemicals comprising those petroleum substances assigned to the established petroleum categories, representative hydrocarbons were selected to predict potential partitioning behavior using simple Level I multimedia modeling equations.

Health Effects

Acute toxicity and Genetic (gene effects) toxicity. EPA agreed that sufficient data were available from all PONA classes for the acute toxicity and genetic (gene) toxicity endpoints for the purposes of the HPV Challenge.

Repeated-dose toxicity. EPA considered that repeated dose studies were adequate for gasoline, high paraffinic, olefinic and aromatic naphthas, and accepted the Test Group's proposal to perform an OECD 422 study to address repeat dose toxicity and developmental/reproductive toxicity for the high naphthenic group.

Genetic toxicity (chromosome effects). EPA raised concerns about the adequacy of the *in vivo* chromosome aberration assay for the high olefinic group.

There were two chromosome aberration tests performed with light catalytic cracked naphtha (LCCN) – one by a single intraperitoneal dose and one by inhalation exposure over 5 days. LCCN did not induce chromosome abnormalities in either study. Unfortunately, these studies were not included in the first IUCLID robust summary submission and perhaps this is the reason for considering this endpoint inadequately addressed. In the supplemental mutagenicity IUCLID data set, submitted to EPA on 8/13/02, the IP study is fully described and the inhalation study was cited. Review of the new robust summary may make these data acceptable.

Developmental Toxicity. EPA requested a separate robust summary to address developmental effects of light alkylate naphtha since the Bui et al. (1998) paper did not provide adequate developmental information.

A new robust summary presenting developmental data for light alkylate naphtha has been prepared from the original study report (Stonybrook Laboratories, Inc. (1995) and has been included in the revised IUCLID data set for the paraffinic group.

Reproductive Toxicity . EPA was concerned that the percentage of aromatics in the distillate of light catalytic reformed naphtha was too low (<10%) to represent the high aromatic naphtha group as described in the test plan (~ 60% aromatic naphthas). The EPA recommended use of a test substance that is representative of the stream.

The light catalytic reformed naphtha reproductive study submitted to represent the high aromatic class contained 33% aromatics and the distilled vapor tested, representing the material to which humans are mostly likely to be exposed, contained >9% aromatics (approximately 5% benzene), a distribution lower than that proposed in the test plan. Aromatic naphthas currently blended into gasoline usually contain approx. 40% aromatic naphtha, less than the 60% cited in the test plan. In the gasoline blending streams average carbon range of C6-C10, only a limited number of aromatic molecules can exist – primarily benzene, toluene, ethylbenzene and xylene (BTEX), for which extensive reproductive and developmental data have been published (see Appendix 1). Given the availability of data on high aromatic naphtha streams aromatic constituents, testing done on gasoline, and data being developed in the international ICCA/American Chemistry Council Hydrocarbon Solvents Test Plan and the Petroleum HPV Testing Consortium Test Plans on hydrocarbon

streams higher in aromatic content, the Testing group considers there is sufficient data to address the reproductive toxicity of high aromatic naphtha streams without performing another inhalation study. Appendix 1 contains a more detailed discussion and summary of data.

Ecotoxicity (fish, invertebrates, and algae).

EPA has proposed that data are needed on the C≥10 end of the carbon range, which is not covered in the PONA approach, and the Testing Group should consider acute and/or chronic tests for aquatic toxicity.

The Testing Group believes that ecotoxicity testing on a C10+ rich sample is unnecessary for this program. Compositional information indicates that the percentage of C10+ components is not significant and will not contribute to aquatic toxicity. Sufficient compositional information has been submitted in robust summaries for representative naphtha samples to support this position.

Specific Comments on the Robust Summaries

Very thorough and useful comments were submitted for individual robust summaries. Summaries and the IUCLID data sets have been revised and expanded to address these comments.

Generic Comment

EPA stated all summaries should clearly identify the test substance, especially in relation to its PONA classification.

Clear descriptions and characterizations of each group and specific test materials have been added. Compositional information has been expanded in Section 1.1 of each IUCLID data set and appropriate references provided in individual summaries.

Health Effects

Repeat Dose Toxicity.

1. Gasoline (subchronic inhalation test with rats and monkeys). Provide the method for generating the test atmosphere and report the magnitude of the observed organ weight changes.

Method for generating test atmospheres has been included. The study report did not provide information on the magnitude of organ wt changes.

2. Olefinic (subchronic inhalation EPA guideline bioassay on light catalytically cracked naphtha distillate; LCCN-D - olefinic content not specified). Provide the method for generating the test atmosphere, and some details such as size of the observed body weight reductions and the incidence of histopathology in nasal turbinates and kidney. Provide the olefinic concentration or specify that the information in dossier section 1.1 pertained to this study.

All comments have been addressed

3. Aromatic (4-week dermal toxicity study of full range catalytically reformed naphtha [FRCRN, sample API 83-05; 62.5% aromatic]). Provide the incidence of increased bone marrow granulopoeisis by dose and sex.

Requested data has been added.

4. Aromatic (13-week rat inhalation study on partially vaporized FRCRN (aromatic content not specified)). Provide the method of generating the test atmosphere, units in the table for the atmosphere components, and the percentage of aromatic naphtha in the test atmosphere. Note that Section 1.1 of the dossier indicated that the aromatics content of distilled or partially vaporized catalytic reformed naphtha may be reduced significantly (to <10% in the distilled fraction); thus, it appears that the aromatic naphtha content did not meet the criterion for a high-naphthenic stream.

Method for generating test material and units have been added. The full range catalytic reformed naphtha (FRCRN) addressed here is a different material from the light catalytic reformed naphtha vapor (LCRN-D) containing <10% aromatics, with a different aromatic content and a different method of chamber atmosphere generation. A discussion of the LCRN study is found earlier in these responses and in Appendix 1.

Genetic Toxicity.

1. (Six robust summaries): Gasoline (Ames test); Gasoline, Olefinic [light cracked catalytic naphtha [LCCN]], Paraffinic [light alkylate naphtha (LAN)], Naphthenic [sweetened naphtha], and Aromatic [full-range catalytic reformed naphtha [FR-CRN]] (forward mutation assay). The source of the S9 activation system is missing and the acronyms TFT and VC were not defined in the LAN and FR-CRN forward mutation assay summaries.

The source of S9 is now identified and definitions for TFT and VC added where appropriate in the robust summaries.

2. Naphthenic [sweetened naphtha] (inhalation in vivo chromosome aberration test). Provide the method for generating the test atmosphere.

Information has been added.

3. Aromatic [full-range catalytic reformed naphtha [FR-CRN]] (in vivo chromosome aberration study). Provide the units in results table, and verify the data because the positive and vehicle control data for the females appear to be reversed.

Corrections have been made.

Reproductive Toxicity.

1. Olefinic (distillate of light catalytically cracked naphtha - LCCN-D) (OECD 421 - combined reproductive/developmental toxicity screening test). Specify the method for generating the test atmosphere or characteristics of the test atmosphere.

Information has been added.

2. Aromatic (distillate of light catalytically reformed naphtha - LCRN -D) (OECD 421). Information provided in dossier section 1.1 suggests that the aromatic content is 9.09%, considerably less than the proposed ~60% content to represent the high end for this subgroup of the category. In addition, the summary reported the actual high dose concentration as 2490 ppm, which may be a typographical error.

Typographical error has been corrected. For discussion of LCRN-D, see earlier responses and Appendix 1

Developmental Toxicity. Olefinic (light catalytically cracked naphtha - LCCN). The summary did not define the numbers in parentheses in the last table and did not report whether food consumption was monitored.

Numbers in parentheses have been defined. Food consumption was not reported in the publication.

Ecological Effects

The submitter needs to provide the missing robust summaries for the data discussed on page 21 of the test plan. These are: the high naphthenic, light straight run naphtha (Concawe sample W94/809) - three summaries; aromatic, light catalytic reformed naphtha CAS #647741-63-5, Concawe sample W94/812) - two summaries. (NOTE: All these appear to come from a single report identified as Concawe, Acute Aquatic Toxicity of Gasolines, Report No. 96/57).

Citations for the ecotoxicity studies have been included in the test plan, however, since the data review has already been conducted by scientific experts in the Concawe organization, no additional review will be done. Due to the lack of experimental detail in the published Concawe report, the Testing Group is unable to assign a Klimisch reliability score to the report. However, the Testing Group thinks the information is consistent with similar tests on other similar petroleum hydrocarbons in these categories and is of sufficient quality to allow it to be used to fulfill the data needs for these endpoints.

In addition, the three naphthenic ecotoxicity robust summaries in which lethality was estimated by the hydrocarbon block method should be more explicit about the input values (i.e., the percent aromatic content and the toxicity factors used for each contributing component)

Additional information regarding the percent of each hydrocarbon has been clarified for this estimation. Adequate information regarding the reference source of respective toxicity endpoints (LC50/EC50 values) is cited in Appendix 3 of the test plan in the discussion of CALCULATION OF ACUTE TOXICITY FROM COMPOSITION.

Closing Remarks

The Testing Group appreciates the EPA, ED and PCRM comments and interest in the gasoline blending streams testing program. It believes that the revised test plan, being submitted via this letter, is both scientifically sound and meets the spirit of the EPA's guidance on animal welfare. The revised test plan makes every effort to minimize the number of animals used in toxicity testing, while at the same time allowing the sponsors to fulfill their product stewardship responsibilities.

If you have further questions or comments about the program, please call me (Lorraine) at (202) 682-8344, Tom Gray at (202) 682-8480 or visit our website at www.petroleumhpv.org.

Sincerely,

Richard Clark, Ph.D., Chairman
Petroleum HPV Oversight Committee

Lorraine Twerdok, Ph.D.
Petroleum HPV Program Manager

cc (via email):

Karen Florini, ED
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Appendix 1. Response to EPA comments on High Aromatic Naphtha Reproductive Study

To address the reproductive toxicity of the high aromatic naphtha class, EPA recommends performance of another study employing a sample with an aromatic content closer to 60% as described in the test plan. The light catalytic reformed naphtha previously tested and submitted to represent the high aromatic class, contained 33% aromatics, and the distilled vapor contained 9% aromatics, a distribution lower than that proposed in the test plan. The Petroleum HPV Testing Group considered that results of this study would be adequate to complete testing for this category in combination with existing data from other studies. The group suggests that there is sufficient data from this plan and other sources to address the reproductive toxicity of high aromatic gasoline blending streams without performing another study.

First, although the technical definition for the high aromatic PONA class indicates an aromatic content up to 60%, in reality, aromatic naphthas currently blended into gasoline contain approximately 40% aromatics, especially since reduction in aromatic content has been EPA mandated. Perhaps more significant is the fact that most gasoline blending streams have a carbon range generally spanning C6-C10. The number of aromatic molecules that could possibly exist within this carbon range will be limited to what are commonly referred to as "BTEX" compounds (benzene, toluene, ethylbenzene, xylene). At some refineries, C9 aromatics are blended into gasoline in place of a high aromatic stream. These compounds have been the subjects of extensive study.

There are published reproductive data available on the principal aromatic compounds found in a high aromatic naphtha stream – benzene, toluene, xylene and high flash aromatic naphthas (C9) – which can be used to "read-across" for potential toxicity. In general, results indicate that inhalation exposure to these compounds induce minimal systemic (reduced body wt) and no reproductive effects on parental animals and decreased body wt and slight skeletal anomalies associated with reduced body wt, in offspring of each generation. [Fetal mortality was increased only with toluene exposure at 2000ppm, Ono et al., 1996]. Table 1 summarizes some of these studies. These data have been used to develop risk assessments in the US and European Union.

. A two-generation reproduction study on a European vapor recovery unit gasoline at concentrations as high as 7400ppm, did not produce adverse reproductive effects on parental animals or offspring in either generation. In addition, a two-generation reproduction study of "industry average" gasoline vapor is being performed under the EPA 211(b) fuel and fuel additives test program. Since the main use for high aromatic naphtha streams is blending into gasoline, these results are relevant in assessing "real world' reproductive toxicity of streams in this category. The ICCA/American Chemistry Council's Hydrocarbon Solvents panel has performed a reproductive toxicity study on C10-C12 aromatic solvent as part of their international HPV test program.

The HPV Petroleum Testing Consortium is developing a range of test plans to address potential toxicity of categories over the continuum of hydrocarbon streams. Reproductive data already available and tests proposed/in progress on mid-range distillates, lubricant base stocks and aromatic oils can be applied to identification of hydrocarbons and hydrocarbon mixtures that may be reproductive toxicants, and the distribution and concentrations necessary for biological effects.

The growing volume of data on possible reproductive toxicity of petroleum streams and published studies on major components of high aromatic blending streams, should be sufficient to allow a reasoned assessment of reproductive potential from the high aromatic naphtha category of gasoline blending streams without performance of another study.

Summary of High Aromatic Studies for Reproductive Toxicity: Effect Levels & Exposure Duration

Test material	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Gasoline 2-generation	Rats – males & females/Inhalation	7400ppm	No reproductive or fertility effects; no effects on offspring survival or growth	OECD protocol #416; OPPTS 870.3800 (1994) [0, 1850, 3700, 7400ppm]	McKee et al., 2000
Benzene 2-generation	Rat – female/inhalation	No maternal effects	116ppm- dec. pup wt no malformations	4 mon prior to impregnation & gestation; 2 generations	Vozovaya, 1975, 1976
1-generation	Rat- female/inhalation	No maternal effects 30ppm	300ppm – dec pup wt, no malformations	6h/d, 5d/wk for 60 d; 7d/wk for 35 days GD 1-20; LD 5-20	Kuna et al., 1992
Toluene Dominant lethal	CD-1 mice – males/ Inhalation	400ppm (max dose) – no effect on sperm, reproduction, embryos	None	6h/d, 5d/wk for 8 wk; then mated for 2wk to untreated F.	Brusick and Mazurksy, 1981
Fertility	SD rats/ inhalation male female	2000ppm (max dose) no effect on fertility; 600ppm	[2000ppm- dec sperm ct., dec wt epididymis] 2000ppm fetal mortality	M – 90 days F – 14 day prior to mating to GD 7, sacr. on GD20	Ono et al, 1996
2-generation	Rats/ inhalation Parental F1 offspring	2000ppm (max dose) – no effect on fertility, repro or lactation (LD) parameters 500ppm	None 2000ppm – dec fetal & pup wt F1 & F2, skeletal effects	6hr/d, 7d/wk; Males 95 days Females 95 d + GD 1-20; LD5-21; F1 offspring same dosing regimen from weaning	API, 1985 Roberts et al., 2003

Summary of High Aromatic Studies for Reproductive Toxicity: Effect Levels & Exposure Duration (cont)

Test material	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Mixed Xylenes 1-generation	Rats- males & females/ inhalation	500ppm – max. dose parents & F1 offspring	None	151d, 5d/wk 35d, 7d/wk, 6hr/d gest. (1-20); lact.(5-20)	API, 1983 1-generation
Male fertility	Rats- Males/ Inhalation	1000ppm – only dose, no effect on testes/acc organs	None	61 days, 18hr/d	Nylén et al., 1989
High Flash Aromatic Naphtha (C9) 3-generation	Rats – males & females/Inhalation offspring	500ppm [no reproductive effects at 1500ppm] 500ppm	1500ppm: dec parental body wt all gen., no repro effects 1500ppm: dec pup body wt all gen. after restart exposure. to dams at lact.day 5 F1 dams with undetected pregnant exposed to delivery had dec. litter size, birth wt and pup survival	10wk, 6hr/d, 5d/wk M&F; F0 6hr/d, 7d/wk GD0-20, LD5-21; F1 GD0-20 begun 5-7wk-old, LD5-21 F2 GD0-20, begun at weaning [3wk old]	McKee et al, 1990
Aromatol (C9) 1-generation	Rats – females/ Inhalation	120ppm	200ppm: maternal & pup body wt dec, also at 400ppm; no malformations	24h/d, 7d/wk GD7-15, natural delivery	Ungváry et al., 1983
	Rats – females/ Inhalation	400ppm	None: did not reproduce Ungváry et al, 1983 effects	24h/d, 7d/wk GD7-15, natural delivery	Lehotzky et al., 1985.
C10-C12 Naphtha	Rats- males & females/Inhalation	In Progress			ICCA Hydrocarbon Solvents HPV Test Program

Appendix 1. References for Table

Gasoline:

McKee, R.H., Trinmer, G.W., Whitman, F.T., Nessel, C.S., Mackerer, C.R., Hagemann, R., Priston, R.A., Riley, A.J., Cruzan, G., Simpson, B.J., Urbanus, J.H. 2000. Assessment in rats of the reproductive toxicity of gasoline from a gasoline vapor recovery unit. *Reproductive Toxicol.* 14: 337-353.

Benzene:

Vozovaya, M.A. 1975. Action of low concentrations of benzene, dischloroethane and their combination on the generative function of animals and the development of progeny. *Gig. Tr. Prox. Label* 7: 20-23 [English abstract].

Vozovaya, M.A. 1976. The effect of small concentrations of benzene and dischloroethane separately and combined on the reproductive function of animals. *G. Sanit* 6: 100-102 [English abstract].

Kuna, R.A., Nicolich, M.J., Schroeder, R. E., and Rusch, G.M. 1992. A female rat fertility study with inhaled benzene. *J Am Coll Toxicol* 11: 275-282.

Toluene:

American Petroleum Institute. 1985. Two-generation inhalation reproduction/fertility study toluene in rats. API Medical Res. Report #32-32854. Washington, DC
Roberts et al., 2003. Reproductive Toxicology (Nov-Dec): in press.

Brusick D.J., and Mazursky S. (1981) Mutagenicity evaluation of toluene. Mouse dominant lethal assay. Litton Bionetics Inc., Kensington, Maryland.

Ono, A., Sekita, K., Ogawa, Y., Hirosa, A., Suzuki, S., Saito, M., Naito, K., Kaneko, T., Furuya, T., Kawashima, K., Yasuhara, K., Matsumoto, K., Tanaka, S., Inoue, T., and Kurokawa, Y. 1996. Reproductive and developmental toxicity studies of toluene. II. Effects of inhalation exposure on fertility in rats. *J. Environ. Pathol. Toxicol. Oncol*. 15: 9-20.

Xylene:

American Petroleum Institute. 1983. Parental and fetal reproduction inhalation toxicity study in rats with mixed xylenes. [performed at Bio/dynamics] API Medical Res. Report #31-31481**.** EPA/OTS FYI-AX-0983-0209. Washington, DC

Nylén, P, Ebendal, T., Eriksdotter-Nilsson, M., et al. 1989. Testicular atrophy and loss of nerve growth factor-immunoreactive germ cell line in rats exposed to n-hexane and a protective effect of simultaneous exposure to toluene or xylene. *Arch Toxicol*. 63: 296-307.

High Flash Aromatic Naphtha (C9)

McKee, R.H., Wong, Z.A., Schmitt, S., Beatty, P., Swanson, M., Schreiner, C.A., and Schardein, J.L. 1990. The reproductive and developmental toxicity of high flash aromatic naphtha. *Toxicol Indust Health* 6: 441-460.

Ungváry, G., Tatrái, E., Lorincz, M., Fittler, Z., and Barcza, G. 1983. Investigation of the embryonic effects of Aromatol, a new C9 aromatic mixture. *Egeszsegtudomany* 29: 138-148. [English abstract]

Lehotzky, K., SzeberenyI, J., Ungváry, G., and Kiss, A. 1985. The effect of prenatal Aromatol exposure on the nervous systems of offspring among rats. *Egeszsegtudomany* 29: 389-397. [English abstract]

Appendix 1. Regulatory Documents

Benzene

Agency for Toxic Substances and Disease Registry (ASTDR). 1993. Toxicological Profile of Benzene. U.S. Dept. of Health and Human Services, U.S. Public Health Service, Atlanta, GA

Agency for Toxic Substances and Disease Registry (ASTDR). 1997. Toxicological Profile of Benzene: Update. U.S. Dept. of Health and Human Services, U.S. Public Health Service, Atlanta, GA

European Union. 2000. Comprehensive risk assessment report of Benzene _EINECS-No. 200-753-7 DRAFT. Rapporteur, German Federal Institute for Occupational Safety and Health Notification Unit

Integrated Risk Information System (IRIS). 1998. Toxicological Review of Benzene (Noncancer effects). NCEA-S-0455. US EPA, Washington, DC.

Toluene

Agency for Toxic Substances and Disease Registry (ASTDR). 1998. Toxicological Profile of Toluene: Update. U.S. Dept. of Health and Human Services, U.S. Public Health Service, Atlanta, GA

European Union, Danish Environmental Protection Agency. 2000. Draft Risk Assessment Report: Toluene, in accordance with Council regulation (ECC 793/93). SIAR 10888.

International Agency for Research on Cancer (IARC). 1989. Some organic solvents, resin monomers and related compounds, pigments, and occupational exposures in paint manufacture and painting. IARC monographs on the evaluation of carcinogenic risk to humans. Vol. 47. IARC, Lyon, France.

IUCLID 1994. IUCLID data sheet, Toluene. Deutsche SHELL Chemie, 30-Jun-1994.

Xylene

Agency for Toxic Substances and Disease Registry (ASTDR). 1995. Toxicological Profile of Xylenes: Update U.S. Dept. of Health and Human Services, U.S. Public Health Service, Atlanta, GA

Integrated Risk Information System (IRIS). 2002. Toxicological Review of Xylenes (CAS #1330-20-7)- Draft. NCEA-S-1203. US EPA, Washington, DC.

International Programme on Chemical Safety (IPCS). 1997. Environmental Health Criteria 190 Xylenes. World Health Organization, Geneva, Switzerland

IUCLID Hedset: para-xylene pp1-49.